## ESR ANALYSIS OF THE KINETIC ALKALINITY OF PSEUDOPHEDRINE

 A. S. Masalimov, S. N. Nikol'skii, A. P. Abdykarimova,
 UDC 543.422.27:541.133.1:

 A. I. Prokof'ev, and Z. M. Muldakhmetov
 547.56:547.233

The kinetics of protonation of pseudoephedrine by 3,6-di-tert-butyl-2-hydroxyphenoxyl have been analyzed by the ESR technique. It was shown that protolysis of the radical produced closed ionic pairs with the pseudoephedrine cation in a dimer state.

Keywords: ESR, pseudoephedrine, 3,6-di-tert-butyl-2-hydroxyphenoxyl, ion pairs.

We previously analyzed a particular kinetic characteristic of thebaine, an alkaloid of the phenanthrene series, a tertiary amine [11]. The interest in pseudoephedrine, a natural base of the ethylamine series, is due to its containing a second nitrogen atom (which determines the NH-acidity of that compound) as well as the hydroxyl group, which acts as a proton donor as well as forming an intramolecular hydrogen bond with the amino group. As an acidic spin probe, the stable semiquinone radical, 3,6-di-*tert*-butyl-2-hydroxyphenoxyl was used (1).

As pseudoephedrine (PE) is a secondary amine, it is only natural to assume that it would exchange the acid NH proton with 1 as in the 1 - diethylamine-toluene system [2]. In this investigation also, toluene was used as a relatively indifferent solvent, dissolving the primary reagents easily. The proton-exchange reaction can be represented in the following way:

The change of spin of the proton of the hydroxyl group 1, which is revealed in the ESR spectrum, in both nature and rate, depends on the dynamics of the  $\mathbf{B} \rightleftharpoons \mathbf{C}$  equilibrium. For the mixture of two OH and NH acids, the rate of spin change of the proton in 1 depends on the lifespan of the closed ion C-type pairs, i.e., on the rate of their decomposition into the primary reaction products.

Figure 1 presents ESR spectra of the 1 – PE-toluene system at different temperatures. The measurements were carried out with an ESR RE-1306 radiospectrometer equipped with a temperature extension. The ESR spectrum of 1 presents a triplet of the doublets with HFI constants of the unpaired electron with the ring and hydroxyl protons, equal, respectively, to  $a_{\rm H} = 0.392$ ,  $a_{\rm H}^{\rm OH} = 0.162$  mT [1]. As can be seen from the ESR spectra, while at high temperatures (300 K and above) one observes a decrease of hydroxyl splitting, characteristic of intermolecular proton exchange, in the intermediate range of 300-253 K there is alteration of the width of the hfs line of the ESR spectrum, typical of rapid, reversible proton transfer from the semiquinone radical 1 to the tertiary base [1]:

$$\dot{Q}H + NR_{3} \rightleftharpoons \dot{Q}H \dots NR_{3} \rightleftharpoons \ddot{Q}H\dot{N}R_{3} \rightleftharpoons \ddot{Q}SH\dot{N}R_{3},$$

$$A(A') \qquad B(B') \qquad C(C') \qquad D(D')$$
(2)

where S are the molecules of the solvating solvent.

Tautomeric forms of all geometrically equivalent radical formations are presented in brackets. Since the measurements were conducted on solutions of 1 in toluene, with a pseudoephedrine concentration of  $[PE] = 10^{-2}$  mole/liter, and there is no significant solvation by the medium, this spectrometric situation can be classified as dynamics of the equilibrium  $A \rightleftharpoons C$   $(A' \rightleftharpoons C')$ .

A. N. Nesmeyanov Institute of Elementoorganic Compounds, Russian Academy of Sciences, 117813 Moscow. Translated from Izvestiya Akademii Nauk, Seriya Khimicheskaya, No. 9, pp. 2007-2011, September, 1992. Original article submitted November 11, 1991.



Fig. 1. ESR spectra of the radical 1 - pseudoephedrine system at different temperatures (K): a) 361; b) 270; c) 189 (with toluene as solvent).

Fig. 2. Arrhenius functions of the decomposition rate and equilibrium constants for the proton transfer reaction from the radical 1 to pseudoephedrine.

TABLE 1. Kinetic and Thermodynamic Characteristics of Proton Transfer from 3,6-ditert-Butyl-2-hydroxyphenoxyl to the Bases

Base	]ıKa	K <sub>b</sub> (293 K), mole <sup>-1</sup>		48, J·mole <sup>-1</sup> ·K <sup>-1</sup>	<pre>k, (293 K), liter-mole<sup>-1</sup>. sec<sup>-1</sup></pre>	$h_0$ . liter.mole <sup>-1</sup> . sec <sup>-1</sup>	E₁∓4.0, kJ*mole <sup>-1</sup>	k-₁ (293 K), sec <sup>-1</sup>	k₀, sec <sup>-1</sup>	E-172.0, kJ*mole <sup>-1</sup>
Trimethyl- amine Thebaine	10,9	9.7	37.7	108.1	7.7·10 <sup>8</sup>	5.4.1010	10.5	8.7-107	3.4.1016	48.2
Pseudophe- drine	7.0 9.8	1.9 11.3	25.3 8.2	81.7 7.8	5.4·10 <sup>8</sup> 1.8·10 <sup>9</sup>	5.1.10 <sup>11</sup> 1.7·10 <sup>13</sup>	10.8 28.0	5.0.10° 1.5.108	4.4.1013	36.2

At 250 K and below, a triplet with  $a_{\rm H} = 0.335$  mT is observed, corresponding to the closed ion pairs of 3,6-di-*tert*-butyl-ortho-semiquinone with the pseudoephedrine cation.

Thus it can be seen from the dynamic ESR spectra that PE can act as a secondary or a ternary base, depending on circumstances.

Figure 2 presents Arrhenius functions for the rate and equilibrium constants of proton transfer from 1 to PE, calculated using the known, modified Bloch equations [3]:

$$\Delta (1/T_2) = \frac{\gamma_e \alpha (1-\alpha) (\Delta a)^2}{k_{-1} + k_1 [\text{PE}]}, \qquad (3)$$

where  $\Delta(1/T_2)$  is the broadening of the extreme right-hand hfs component of the ESR spectrum for 1;  $\Delta a$  is the distance between that and the adjacent line, also broadened, mT;  $\alpha$  and  $(1 - \alpha)$  are molar fractions of the A(A') and C(C') particles;  $k_1 = k_{AC} + k_{A'C'}$  and  $k_{-1} = k_{CA} + k_{C'A'}$  are specific rates of the direct and reverse reactions of proton transfer; and  $\gamma_e$  is the gyromagnetic ratio for an electron.



Fig. 3. ESR spectra of the ionic pairs of the radical 1 with the pseudoephedrine cation at different temperatures (K): a) 223; b) 195 (at a higher resolution); c) 235 K (toluene used as the solvent).

The equilibrium constant  $(K_e, \text{ liter} \cdot \text{mole}^{-1})$  for reaction (1) was calculated from the change of hydroxyl splitting  $\bar{a}$  in the ESR spectrum of the semiquinone radical [1]:

$$K_{\rm e} = \frac{a_0 - \bar{a}}{\bar{a} \left[ {\rm PE} \right]} \,, \tag{4}$$

where  $a_0$  is the HFI constant for the unpaired electron with the hydroxyl proton 1, in the absence of PE from the solution, equal to 0.162 mT.

Table 1 presents kinetic and thermodynamic characteristics of the proton transfer from 1 to PE, obtained from the dynamic ESR spectra. Similar characteristics for tertiary amines with known  $pK_{\alpha}$ , produced previously by the present authors, are also presented in Table 1 for comparison. The fact that pseudoephedrine, which is a 1,2-amino alcohol or a three isomer of 1-phenyl-2-methylaminopropanol-1, reveals properties of the tertiary amine, is apparently caused by an intramolecular hydrogen bond (IHB) between the neighboring OH and NH acid groups [4]. As NH acidity of aliphatic secondary amines is usually stronger than the OH acidity of the corresponding alcohols, it can be assumed that the NH proton is sufficiently bonded by IHB in PE. The protonation of the secondary nitrogen atom in PE in the place of localization of its unshared pair of electrons does not cause the disintegration of IHB because, if it did, in the above-mentioned temperature region in the ESR spectrum of 1, reorientation of the proton spin would occur due to the intermolecular exchange. As can be seen from Table 1, the kinetic and thermodynamic alkalinities of PE ( $K_p$  and  $k_1$ ) are close to the similar characteristics for 3-ethylamine. However, because the atom is involved in the formation of IHB, the activation barrier of its protonation ( $E_1$ ) is approximately three times lower than that for 3-ethylamine. Apparently that also explains the low thermal effect of the reaction.

As was mentioned previously, at 300 K and above, in the ESR spectrum of the 1 - PE-toluene system there is a decrease of the doublet splitting  $\tilde{a}$ , which is caused by the quick proton exchange (1). The rate of the proton-exchange reaction between 1 and PE can be determined from the following formula [2, 3]:

$$v_{ex} = \frac{\gamma_c a_0}{2\sqrt{2}} \sqrt{1 - \left(\frac{\bar{a}}{a_0}\right)^2} .$$
 (5)

The rate constant of reaction (5),  $k_{ex} = 4\nu_{ex}/[PE]$ , assessed from the ESR spectra, is  $k_{ex} = 2.1 \cdot 10^{13} \exp \left[-(26,000 \mp 4000)\right]/RT$  liter mole<sup>-1</sup>·sec<sup>-1</sup>;  $k_{ex}$  (293 K) =  $4.6 \cdot 10^8$  liter mole<sup>-1</sup>·sec<sup>-1</sup>. Apparently, during heating of the reaction mixture, IHB disintegrates and the exchange of protons between the OH acid (radical) and NH acid (pseudoephedrine) becomes possible. As the rate of this reaction is controlled by the stage of proton transfer from 1 to PE, as can be seen from the above data, kinetic parameters of the proton exchange do not exceed in value the specific rate and the energy value of pseudoephedrine protonation.

At low temperatures (220 K and below), as the equilibrium (2) shifts to the left, in the ESR spectrum of the 1-PE-toluene, a triplet with  $a_{\rm H} = 0.335$  mT appears. It corresponds to the closed ion pair of semiquinone anion-radical and pseudoephedrine cation. The broadening of the central component of the triplet is related to the decreased rate of the degenerate cation attraction  $\mathbf{C} \rightleftharpoons \mathbf{C}'$ . The rate and activation energy of the cation attraction are:  $\nu_{\rm ex}(213 \text{ K}) = 1.6 \cdot 10^7 \cdot \sec^{-1}$ ,  $E_a = 6.2$  kJ/mole. Figure 3 presents the superposition of two ESR spectra produced while the capsule with the sample was held at 220 K for 10-15 min. Apart from the above-mentioned triplet, a triplet of quintets with  $a_{\rm H} = 0.340$  and  $a_{\rm N} = 0.06$  mT appear. The quintet is caused by hyperfine interaction of the unpaired electron with two magneto-equivalent nitrogen nuclei  $(J_{14_{\rm N}} = 1)$ , and it is displaced into a stronger field. This effect can be explained by dimerization of closed ion pairs at the state:  $2C \neq C_2$  ( $2C' \neq C_2'$ ). The authors recorded a similar effect for ion pairs of 3,6-di-*tert*-butyl-*ortho*-semiquinone with the cations of alkali metals [5].

## REFERENCES

- 1. A. S. Masalimov, S. N. Nikol'skii, A. P. Abdykarimova, A. I. Prokof'ev, and A. I. Muldakhmetov, *Izv. Akad. Nauk KazSSR, Ser. Khim.*, No. 2, 15 (1989).
- 2. A. S. Masalimov, A. I. Prokof'ev, S. P. Solodovnikov, N. N. Bubnov, and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 4, 767 (1977).
- 3. A. Carrington and A. D. MacLachlan, Introduction to Magnetic Resonance: With Applications to Chemistry and Chemical Physics, [Russian translation], Mir, Moscow (1970), p. 266.
- 4. M. Zh. Zhurinov, A. M. Gazaliev, and S. D. Fazylov, *Chemistry of Ephedrine Alkaloids* [in Russian], Nauka, Alma-Ata (1990), p. 5.
- 5. A. S. Masalimov, O. D. Kemalov, É. K. Zhumadilov, and A. I. Prokof'ev, Luminescence and Study of Radiation Parameters [in Russian], Karaganda (1987), p. 74.